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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 31/71, 31/33	A1	(11) International Publication Number: WO 93/14771 (43) International Publication Date: 5 August 1993 (05.08.93)
(21) International Application Number: PCT/GB93/00207 (22) International Filing Date: 1 February 1993 (01.02.93) (30) Priority data: 9202196.3 1 February 1992 (01.02.92) GB (71) Applicant (for all designated States except US): FISON'S PLC [GB/GB]; Fison House, Princes Street, Ipswich, Suffolk IP1 1QH (GB). (72) Inventor; and (75) Inventor/Applicant (for US only) : ORR, Thomas, Samuel, Campbell [GB/GB]; Crespina, Melton Road, Waltham on the Wolds, Melton Mowbray, Leicestershire LE14 4AJ (GB). (74) Agent: WRIGHT, Robert, Gordon, McRae; Fisons plc, 12 Derby Road, Loughborough, Leicestershire LE11 0BB (GB).		(81) Designated States: AU, BB, BG, BR, CA, CZ, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: MACROCYCLIC COMPOUNDS IN THE PROPHYLACTIC TREATMENT OF AIDS (57) Abstract There is provided the use of derivatives and homologues of 12-(2-cyclohexyl-1-methylvinyl)-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0 ^{4,9}]octacos-18-ene in the prophylactic treatment of AIDS.		

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Macrocyclic compounds in the prophylactic treatment of AIDS

This invention relates to a new use of known macrocyclic compounds in the prophylactic treatment of acquired immunodeficiency syndrome (AIDS).

AIDS is characterized by a degeneration of the patient's immune system, making the patient susceptible to opportunistic infections such as pneumonia which generally lead to death.

Current theory suggests that the human immunodeficiency virus (HIV) causes AIDS. However, patients infected with HIV can remain healthy for several years before developing the symptoms of AIDS.

The drugs presently administered to patients infected with HIV and to patients suffering from AIDS include 3'-azido-3'-deoxythymidine (AZT, Retrovir), which interferes with viral replication. However, it is frequently toxic, and after a few months of treatment AZT-resistant mutants of HIV appear (Karpas *et al*, Proc Natl Acad Sci USA, 89, pp8351-8355). Furthermore, patients infected with HIV who are treated with AZT generally go on to develop AIDS eventually.

There is therefore a need for a drug which is effective or more effective in the prophylactic treatment of AIDS (by which we mean that the treatment defers the onset of AIDS in patients infected with HIV), which is less toxic than current therapies, and which can be used in patients who have grown resistant to treatment with AZT.

European Patent Application 184162 discloses a number of macrocyclic compounds which are indicated as immunosuppressants. The compounds may be described as derivatives and homologues of the basic structure 12-(2-cyclohexyl-1-methylvinyl)-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene, and include 17-allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone (FR-900506, FK 506) and 16-allyl-1,13-dihydroxy-11-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-22,24-dimethoxy-12,18,20,26-tetramethyl-10,27-dioxa-4-

azatricyclo [21.3.1.0^{4,8}]octacos-17-ene-2,3,9,15-tetraone (FR-900525). Many other macrocyclic compounds of this class have since been disclosed, both synthetically derived from the compounds of European Patent Application 184162 (see International Patent Application WO 89/05304) and from fermentation (see European Patent Applications
5 349049 and 349061).

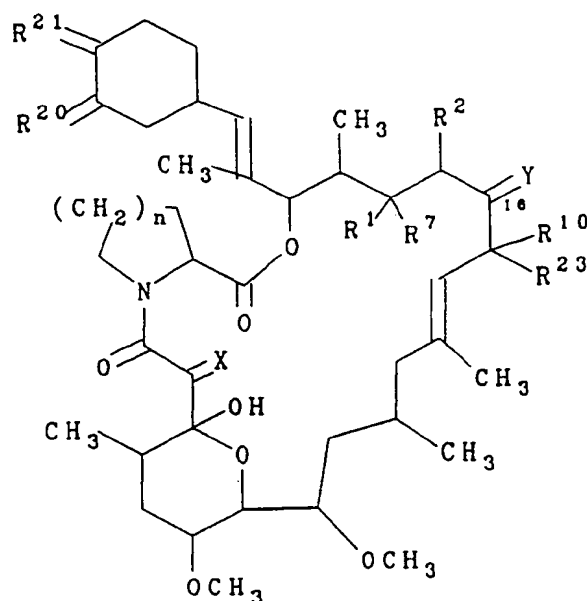
International Patent Application No WO 91/04025 discloses a number of macrocyclic compounds believed to be antagonists of the compound FR-900506 in the treatment of diseases involving immunodepression, and AIDS is mentioned generally. However, there
10 is no suggestion of any prophylactic activity.

It has now been found that derivatives or homologues of the basic structure 12-(2-cyclohexyl-1-methylvinyl)-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene are useful in the prophylactic treatment of AIDS.
15

Thus, according to the present invention, there is provided the use of a derivative or homologue of 12-(2-cyclohexyl-1-methylvinyl)-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene as active ingredient in the manufacture of a medicament for the prophylactic treatment of AIDS.
20

A group of such derivatives or homologues which may be mentioned are those having immunosuppressive activity. It is especially unexpected that compounds having this activity find utility in the prophylaxis of AIDS.

25 A preferred group of derivatives or homologues which may be mentioned are the compounds of formula I,



wherein the vicinal pair of substituents [R^1 and R^2] represent two vicinal hydrogen atoms, or form a second bond between the vicinal carbon atoms to which they are attached;

5 R^7 represents H, OH, protected hydroxy or alkoxy C_{1-6} ;

R^{10} represents alkyl C_{1-6} or alkenyl C_{2-6} ;

X represents O, (H,H), (H,OH) or $-CH_2O-$;

Y represents O, $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R^{11} and R^{12} independently represent H, alkyl C_{1-6} , phenyl or tosyl;

10 R^{13} represents H or alkyl C_{1-6} ;

R^{20} and R^{21} independently represent O, or they may independently represent (R^{20a} ,H) and (R^{21a} ,H) respectively; R^{20a} and R^{21a} independently represent OH, protected hydroxy, alkoxy C_{1-6} or $OCH_2OCH_2CH_2OCH_3$; in addition R^{20a} and R^{21a} may together represent an oxygen atom in an epoxide ring;

15 R^{23} represents H;

n is 1 or 2;

in addition to their significances above, Y, R¹⁰ and R²³, together with the carbon atoms to which they are attached, may represent a 5- or 6-membered N-, S- or O-containing heterocyclic ring, which may be saturated or unsaturated, and which may be substituted by one or more groups selected from alkyl C₁₋₆, hydroxy, alkyl C₁₋₆ substituted by one or more hydroxy groups, alkoxy C₁₋₆, benzyl and -CH₂Se(C₆H₅);
in addition, when the vicinal pair of substituents [R¹ and R²] represent two vicinal hydrogen atoms, then R⁷ and Y may together represent the group -O-N(O)_m= wherein the N atom is bonded to C16 and m is 0 or 1;
and pharmaceutically acceptable salts thereof.

10

Pharmaceutically acceptable salts of the compounds of formula I include acid addition salts (for example hydrochloride), of any amine groups present.

Compounds of formula I in which X is (H,H) are known from International Patent Application No WO 91/02736. Compounds of formula I in which R⁷ and Y together represent the group -O-N(O)_m= are known from International Patent Application No WO 92/03441.

Preferred groups of compounds of formula I include those in which:

20 R¹⁰ represents methyl, ethyl, propyl or allyl;

at least one of R^{20a} and R^{21a} represents OH or OCH₃;

n is 2;

any ring formed by Y, R¹⁰ and R²³ is a pyrrole or tetrahydrofuran ring; and

R⁷ is H or OH.

25

Specific derivatives of 12-(2-cyclohexyl-1-methylvinyl)-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene which may be mentioned include:

17-Allyl-1,14,20-trihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-
2,3,10,16-tetraone,

30

17-Ethyl-1,14,20-trihydroxy-12-[2-(3,4-dihydroxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone,

17-(1-Hydroxyprop-2-enyl)-1,14,20-trihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone,

17-(2,3-Dihydroxypropyl)-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone,

17-Ethanyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone,

17-Allyl-1,2,14,16-tetrahydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-3,10-dione, and

17-(2-Oxopropyl)-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone,

this latter compound being of particular interest.

Specific immunosuppressive derivatives of 12-(2-cyclohexyl-1-methylvinyl)-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene which may be mentioned

include:

17-Allyl-1,2,14-trihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-3,10,16-trione,

17-Propyl-1-hydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone,

17-Allyl-1-hydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone,

17-Ethyl-1,14-dihydroxy-12-[2-(3,4-dihydroxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone,

17-Allyl-1,14-dihydroxy-12-[2-(3,4-dihydroxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone,

17-Ethyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone (FR-900520), and

17-Allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone (FR-900506),

this latter compound being of particular interest.

The derivatives and homologues for use in the invention may be administered by any convenient means. For example, they may be introduced parenterally by injection eg intravenously, intramuscularly or subcutaneously; orally; by inhalation eg in the form of a pressurised or non-pressurised powder formulation; topically; or by plasmapheresis.

Examples of suitable adjuvants, diluents or carriers are:

for tablets, capsules and dragees - microcrystalline cellulose, calcium phosphate, diatomaceous earth, lactose, starch, talc or stearic acid;

for injectable solutions - water, alcohols, glycerin or vegetable oils;

for inhalation compositions - lactose.

The compositions may also contain suitable preserving, stabilising and wetting agents, solubilisers (eg a water-soluble cellulose polymer such as hydroxypropyl methylcellulose, or a water-soluble glycol such as propylene glycol), sweetening and colouring agents and flavourings. The compositions may, if desired, be formulated in sustained release form.

The dosage administered will vary with the compound employed and the mode of administration. However, in general, satisfactory results are obtained when the compounds are administered at a dosage which produces a concentration in the blood stream of from 0.1-150 µg/ml, preferably 1-150 µg/ml.

For man the indicated total daily dosage is in the range of from 0.1mg to 3000mg and preferably from 1mg to 2000mg, which may be administered, for example, in divided doses from 1 to 6 times a day or in sustained release form.

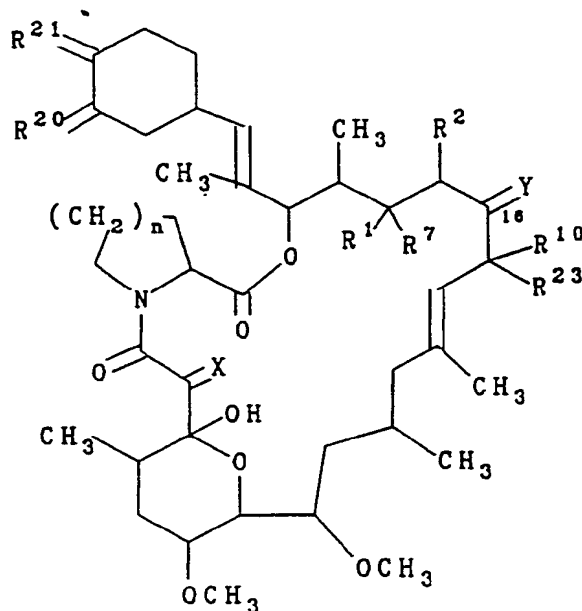
- 5 According to a further aspect of the invention, there is provided a method of prophylaxis of AIDS, which comprises administering a therapeutically effective amount of a derivative or homologue of 12-(2-cyclohexyl-1-methylvinyl)-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene to a patient infected with HIV.

10 Biological Activity

The biological activity of the derivatives and homologues for use in the invention may be demonstrated using the methods disclosed by Karpas *et al*, Proc Natl Acad Sci USA, 89, pp8351-8355. Karpas *et al* demonstrated therein that FR-900506 interferes with HIV production and selectively inhibits the growth of uninfected cells.

Claims:

1. The use of a derivative or homologue of 12-(2-cyclohexyl-1-methylvinyl)-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene as active ingredient in the manufacture of a medicament for the prophylactic treatment of AIDS.
2. The use as claimed in claim 1, wherein the derivative is an immunosuppressant.
3. The use as claimed in claim 1 or claim 2, wherein the derivative is a compound of formula I,



wherein the vicinal pair of substituents [R¹ and R²] represent two vicinal hydrogen atoms, or form a second bond between the vicinal carbon atoms to which they are attached;

- 15 R⁷ represents H, OH, protected hydroxy or alkoxy C₁₋₆;
- R¹⁰ represents alkyl C₁₋₆ or alkenyl C₂₋₆;

X represents O, (H,H), (H,OH) or $-\text{CH}_2\text{O}-$;

Y represents O, $\text{N}-\text{NR}^{11}\text{R}^{12}$ or $\text{N}-\text{OR}^{13}$;

R^{11} and R^{12} independently represent H, alkyl C_{1-6} , phenyl or tosyl;

R^{13} represents H or alkyl C_{1-6} ;

5 R^{20} and R^{21} independently represent O, or they may independently represent (R^{20a}, H) and (R^{21a}, H) respectively; R^{20a} and R^{21a} independently represent OH, protected hydroxy, alkoxy C_{1-6} or $\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$; in addition R^{20a} and R^{21a} may together represent an oxygen atom in an epoxide ring;

R^{23} represents H;

10 n is 1 or 2;

in addition to their significances above, Y, R^{10} and R^{23} , together with the carbon atoms to which they are attached, may represent a 5- or 6-membered N-, S- or O-containing heterocyclic ring, which may be saturated or unsaturated, and which may be substituted by one or more groups selected from alkyl C_{1-6} , hydroxy, alkyl C_{1-6} substituted by one or
15 more hydroxy groups, alkoxy C_{1-6} , benzyl and $-\text{CH}_2\text{Se}(\text{C}_6\text{H}_5)$;

in addition, when the vicinal pair of substituents [R^1 and R^2] represent two vicinal hydrogen atoms, then R^7 and Y may together represent the group $-\text{O}-\text{N}(\text{O})_m=$ wherein the N atom is bonded to C16 and m is 0 or 1;
or a pharmaceutically acceptable salt thereof.

20

4. The use as claimed in claim 3, wherein R^{10} represents methyl, ethyl, propyl or allyl.

5. The use as claimed in claim 3 or claim 4, wherein at least one of R^{20a} and R^{21a}
25 represents OH or OCH_3 .

6. The use as claimed in any one of claims 3 to 5, wherein n is 2.

7. The use as claimed in claim 3, wherein any ring formed by Y, R^{10} and R^{23} is a
30 pyrrole or tetrahydrofuran ring.

8. The use as claimed in claim 1, wherein the derivative of 12-(2-cyclohexyl-1-methylvinyl)-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene is:

- 17-Allyl-1,14,20-trihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-
s dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-
2,3,10,16-tetraone,
17-Ethyl-1,14,20-trihydroxy-12-[2-(3,4-dihydroxycyclohexyl)-1-methylvinyl]-23,25-
dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-
2,3,10,16-tetraone,
10 17-(1-Hydroxyprop-2-enyl)-1,14,20-trihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-
methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-
azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone,
17-(2,3-Dihydroxypropyl)-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-
methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-
15 azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone,
17-Ethanalyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-
dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-
2,3,10,16-tetraone,
17-Allyl-1,2,14,16-tetrahydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-
20 23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-
ene-3,10-dione, or
17-(2-Oxopropyl)-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-
23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-
ene-2,3,10,16-tetraone.

25

9. The use as claimed in any one of claims 1 to 3, wherein the derivative of 12-(2-cyclohexyl-1-methylvinyl)-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene is:

- 17-Allyl-1,2,14-trihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-
30 dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-
3,10,16-trione,

17-Propyl-1-hydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone,

17-Allyl-1-hydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone,

17-Ethyl-1,14-dihydroxy-12-[2-(3,4-dihydroxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone,

17-Allyl-1,14-dihydroxy-12-[2-(3,4-dihydroxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone,

17-Ethyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone, or

17-Allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone.

10. A method of prophylaxis of AIDS, which comprises administering a therapeutically effective amount of a derivative or homologue of 12-(2-cyclohexyl-1-methylvinyl)-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene to a patient infected with HIV.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 93/00207

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl. 5 A61K31/71; A61K31/33		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	AIDS RES. HUM. RETROVIRUSES vol. 8, no. 5, 1992, page 910 P. HÖLLSBERG ET AL. 'HTLV-I induced spontaneous T-cell clonal proliferation is rapamycin sensitive' see abstract	1-10
O,A	& Annual Meeting on Aids Research and Human Retroviruses, Bethesda, Maryland, USA September 1-8, 1991 <div style="text-align: center; margin-top: 10px;"> --- -/-- </div>	1-10
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
26 MAY 1993		22.06.93
International Searching Authority		Signature of Authorized Officer
EUROPEAN PATENT OFFICE		FOERSTER W.K.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P,X	<p>PROC. NATL. ACAD. SCI. USA vol. 89, September 1992, pages 8531 - 8355 A. KARPAS ET AL. 'Inhibition of human immunodeficiency virus and growth of infected T cells by the immunosuppressive drugs cyclosporin A and FK 506' cited in the application see the whole document -----</p>	1-10

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